Citation:

Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LC. Impact of folic acid fortification on the US food supply on the occurrence of neural tube defects. *JAMA.* 2001; 285: 2,981-2,986.

PubMed ID: 11410096

Study Design:

Trend study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To use birth certificate data to evaluate the impact of folic acid fortification on the birth prevalence of neural tube defects (NTD) in the United States.

Inclusion Criteria:

Prevalence of NTDs was obtained from birth certificates meeting the following criteria:

- Certificates from 45 states and Washington DC
- Certificates from January 1990 to December 1999.

Exclusion Criteria:

Birth certificates from five states were excluded for the following reasons:

- Birth certificates from New Mexico, New York and Oklahoma did not report congenital anomalies for one or more years during the time period studied
- Birth certificates from Connecticut and Maryland did not state congenital anomaly status for more than 25% of births during several years between 1990 and 1999.

Description of Study Protocol:

Recruitment

Birth certificate information is collected by state vital statistic offices and compiled by the CDC's National Center for Health Statistics.

Design

- The birth prevalence of NTDs during the post-fortification period (October 1998 to December 1999) was compared with prevalence during both the period immediately prior to fortification (October 1995 to December 1996) and from 1990 to 1995
- Prevalence from the post-fortification period was compared with both these two time periods as references to assess if any decrease was dependent on choice of reference group
- Prevalence among women who began prenatal care in the third trimester or who received no prenatal care was also evaluated.

Intervention

Mandatory fortification of cereal products in the United States.

Statistical Analysis

- Differences in prevalence of spina bifida and anencephaly between the groups were expressed as prevalence ratios (PRs) and 95% confidence intervals (calculated using Epi Info). The ratio was determined by dividing the number of infants diagnosed with either birth defect by the total number of live births during the same time period
- The exponential weighted moving average (EWMA) was used to determine the timing of statistically significant changes in prevalence from the baseline mean (baseline mean was based on the 1990 to 1996 data). Parameters for the EWMA analysis were set at α=0.01 and the weight was set at 0.075 to yield an average run length of 25 years (indicating that only one false out-of-control signal should occur every 25 years of data analyzed. The EWMA analysis was used to detect timing of statistically significant shifts from the mean quarterly prevalence of spina bifida and anencephaly. Six-month intervals were used for the analysis of NTD prevalence for women receiving only third trimester care or no prenatal care as well as the analysis for total NTD prevalence among all births
- An analysis to determine the overall sensitivity of birth certificates to birth defects during this time period was also conducted by calculating the percentage of certificates noting at least one congenital abnormality. The authors concluded that the positive predictive value of NTDs as reported on birth certificates is high, indicating that true NTD trends are being observed.

Data Collection Summary:

- *Timing of measurements:* Data on NTDs was recorded on birth certificates
- *Dependent variables:* Prevalence of NTDs, particularly spina bifida and anencephaly
- *Independent variables:* Folic acid fortification of cereal products in the United States
- *Control variables:* A subgroup analysis was conducted among women receiving no or limited (third trimester only) prenatal care.

Description of Actual Data Sample:

- *Age:* Birth certificate data
- *Location:* Multi-state study in the United States.

Summary of Results:

Table 1: Birth Prevalence During the Pre-fortification Time Period (October 1995 to December 1996) and the Post-fortification Time Period (October 1998 to December 1999) in the United States (Per 100,000 Births)

	Spina Bifida	Anencephaly	Total NTDs
Pre-fortification	26.2	11.6	37.8
Post-fortification	20.2	10.3	30.5

Prevalence of spina bifida declined 23% during this time period, while anencephaly prevalence declined 11%. Total NTD prevalence dropped 19%. Declines in spina bifida and total NTDs were similar using either reference group; however, the decline in anencephaly prevalence was greater when the entire pre-fortification period was used as a reference.

Table 2: Effect Estimates for the Decline in Observed NTDs During the Post-fortification Period in the United States (Using the Immediate Pre-fortification Period of October 1995 to December 1996 as Reference)

	Spina Bifida		Anencephaly		Total NTDs	
Time Period	**# of Cases**	**Prevalence Ratio (95% CI)**	**# of Cases**	**Prevalence Ratio (95% CI)**	**# of Cases**	**Prevalence Ratio (95% CI)**
October 1998 to December 1999	884	0.77 (0.70 to 0.84)	453	0.89 (0.78 to 1.01)	1,337	0.81 (0.75 to 0.87)
October 1995 to December 1996	1,123	1.00	497	1.00	1,620	1.00

Table 3: Effect Estimates for the Decline in Observed NTDs During the Post-fortification Period in the United States (Using the Entire Pre-fortification Period of 1990 to 1996 as Reference)

	Spina Bifida		Anencephaly		Total NTDs	
Time Period	**# of Cases**	**Prevalence Ratio (95% CI)**	**# of Cases**	**Prevalence Ratio (95% CI)**	**# of Cases**	**Prevalence Ratio (95% CI)**
October 1998 to December 1999	884	0.81 (0.75 to 0.87)	453	0.77 (0.70 to 0.85)	1,337	0.79 (0.75 to 0.84)
1990 to 1996	6,163	1.00	3,329	1.00	9,492	1.00

Findings from the EWMA Analysis

- *Spina bifida:* Overall trends indicate that prevalence has steadily declined since early 1997. A significant increase in prevalence was observed in the fourth quarter of 1996, while significant decreases were observed in the second quarter of 1992, the fourth quarter of 1998 and the second and third quarters of 1999
- *Anencephaly:* The overall trend indicates a higher prevalence from 1990 to 1992, a decline in late 1991 through 1994, stability from 1995 to 1997 and another slight decline from 1998 to 1999. The EWMA analysis showed five significant quarterly increases in 1990 to 1991, three significant decreases from 1994 to 1997, a decrease in the first and fourth quarters of 1998 and the second and fourth quarters of 1999
- *Total NTDs (six-month intervals):* One significant increase was shown from January to June 1991. Three significant decreases were shown during the end of the observed time period (July to December 1998, January to June 1999 and July to December 1999).

Other Findings: Observations Among Women Receiving No or Third-trimester-only Prenatal Care

The magnitude of decline was similar for this subgroup. The observed decline in prevalence was significant (only when compared with the entire pre-fortification period as reference).

EWMA Analysis (Six-month Intervals)

There was no stable trend observed; however, the observed prevalence reached its lowest points during the last half of 1998 and all of 1999.

Table 4: Effect Estimates for the Decline in Observed NTDs During the Post-fortification Period in the United States Among Women Receiving No or Third-trimester-only Prenatal Care (Using the Immediate Pre-fortification Period of October 1995 to December 1996 as Reference)

	Spina Bifida	Anencephaly	Total NTDs

Time Period	# of Cases	Prevalence Ratio (95% CI)	# of Cases	Prevalence Ratio (95% CI)	# of Cases	Prevalence Ratio (95% CI)
October 1998 to December 1999	38	0.71 (0.47 to 1.07)	36	1.14 (0.71 to 1.83)	74	0.87 (0.64 to 1.18)
October 1995 to December 1996	56	1.00	33	1.00	89	1.00

Table 5: Effect Estimates for the Decline in Observed NTDs During the Post-fortification Period in the United States Among Women Receiving No or Third-trimester-only Prenatal Care (Using the Entire Pre-fortification Period of 1990 to 1996 as Reference)

	Spina Bifida		Anencephaly		Total NTDs	
Time Period	# of Cases	Prevalence Ratio (95% CI)	# of Cases	Prevalence Ratio (95% CI)	# of Cases	Prevalence Ratio (95% CI)
October 1998 to December 1999	38	0.71 (0.51 to 0.99)	36	0.89 (0.63 to 1.26)	74	0.79 (0.62 to 1.00)
1990 to 1996	395	1.00	298	1.00	693	1.00

Author Conclusion:

The authors note that a 19% decrease in NTD prevalence was observed post-fortification of the grain supply in the United States. Other factors may have contributed to the observed decline, including the following:

- Validity of birth certificate data; no changes in sensitivity were observed during the observed time period, leading the authors to conclude that the data reflects real changes in NTD prevalence
- Lack of data on NTD-affected pregnancies leading to induced or spontaneous abortions.

Reviewer Comments:

CIs were reported; however, no significance level was reported.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes

2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???

3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	N/A
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	N/A
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	No
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	No
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	No

6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	No
6.6.	Were extra or unplanned treatments described?	No
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes

9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes